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| EXAMINER | |
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| ANDERSON, JAMES D | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

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| ***Office Action Summary*** | **Application No.**<br>10/682,662 | **Applicant(s)**<br>TAS ET AL. | |
| | **Examiner**<br>JAMES D. ANDERSON | **Art Unit**<br>1614 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,8,9,11,27,28 and 31-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,9,11,27,28, 31, 33, 35, and 37-52* is/are rejected.

7)☒ Claim(s) *32,34 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claims 1, 8-9, 11, 27-28, and 31-52 are presented for examination*

Applicants' amendment filed 12/18/2007 has been received and entered into the application. Accordingly, claims 31-52 have been added.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Change of Examiner*

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

### *Response to Arguments*

Applicant's arguments filed 12/18/2007 have been fully considered but they are not persuasive. In traversing the rejections set forth in the previous Office Action, Applicants present the following arguments.

Claims 1, 8, 9, 11, 27, and 28 were rejected under 35 U.S.C. 112, 1st paragraph (Written Description) as lacking adequate description for the recited "derivatives" of cyclopamine.

Applicants first assert that *Rochester* supports their arguments that an already described class of compounds known to have properties in common can be claimed by recitation of those shared properties. While it is true that in *Rochester* there was a lack of any known members of the claimed class and that the court held that the exact chemical component of each combination that falls within the claims in not necessary to comply with 112, the fact remains that in the instant case, the claims recite active agents that are defined only by the fact that they are "derivatives” of cyclopamine, with no disclosure of any chemical structures or specific modifications that may be made to cyclopamine. Further, newly added claims recite active agents that are defined only by their biological activity. As such, given the fact that Applicants only disclose cyclopamine and jervine, it is not seen that the specification provides written basis for the active agents recited in the instant claims.

Further, while other non-cyclopamine molecules may have been "well-known" in the art, the fact remains that Applicants did not describe any of these "well-known" molecules and have provided no evidence that these molecules exert receptor-binding properties “similar to cyclopamine” and/or “bind to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling” as recited in the instant claims. Further still, the Examiner is not persuaded that these “known” molecules are representative of the entire genus of compounds encompassed by the present claims.

Applicants further argue that a compound defined as a compound that “specifically inhibits Hh/Smo signaling” is understood clearly by a person skilled in the art. The Examiner is not persuaded by this argument because while compounds may well be known that inhibit Hh/Smo signaling, no evidence has been provided that these known compounds are *specific* inhibitors of Hh/Smo signaling (*i.e.*, do not substantially inhibit any other biological target).

Applicants further argue that they have provided, in the specification, references to scientific publications referring to proteins and non-cyclopamine molecules that inhibit Hh/Smo signaling. Firstly, a protein is not reasonably a "derivative" of cyclopamine and is thus not reasonably included in Applicants' definition of a “derivative” of cyclopamine. Secondly, there is no evidence of record that the non-cyclopamine molecules referred to in the cited scientific publications are “derivatives” of cyclopamine or exert receptor-binding properties similar to cyclopamine and bind to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling as recited in the instant claims.

Finally, Applicants argue that numerous naturally occurring and synthetic non-cyclopamine molecules with and without a cyclopamine core were well known in the prior art suitable for specifically inhibiting Hh/Smo signaling. As such, citing *Union Oil v. Atlantic Richfield Co.* ("*Unocal*"), Applicants submit that when the skilled person already is familiar with materials having the recited properties "description of the exact chemical component....is not necessary to comply with 112". However, in reviewing the instant application, the Examiner notes that Applicants disclose as their invention “...the use of cyclopamine..." (page 4, line 11); "Therapeutic compositions comprising cyclopamine..." (page 4, line 18); "...the use of cyclopamine or a pharmaceutically acceptable salt thereof or a derivative thereof...” (page 4, lines 24-24; page 5, lines 1-3; page 5, lines 5-6); and “This invention relates to the use of cyclopamine....” (page 14, line 24). As such, no where in Applicants summary of their invention or description of their invention do they disclose that other compounds that “specifically inhibit Hh/Smo signaling” can be used in the invention. While Applicants do disclose that "derivatives of cyclopamine" that “exert similar receptor-binding properties and biological and therapeutic effects as cyclopamine” can be used in the invention (page 17, lines 20-26), Applicants definition of “derivatives of cyclopamine” as disclosed at page 17, line 26 to page 18, lines 16 requires that a derived molecule contain "the region of cyclopamine molecule involved in the binding of cyclopamine to its biological target but contains in addition modifications of the parent cyclopamine molecule" (page 18, lines 1-4). No such derivatives have been identified by Applicants and it is clear that Applicants' definition does not include the proteins disclosed in the prior art.

In view of the above discussion, the Examiner is not persuaded that the instant claims have adequate written support for the claimed “derivatives” of cyclopamine, “another compound that specifically inhibits Hedgehog/Smoothened signaling”, or compounds that “exerts receptor-binding properties similar to cyclopamine and bind to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling”.

### ***Claim Rejections - 35 USC § 112 ($2^{nd}$ Paragraph)***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear from the claims to whom or what the claimed compounds are being administered. In other words, the patient population being treated has not been distinctly claimed.

### *Claim Rejections - 35 USC § 112 (1st Paragraph)*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8-9, 11, 27-28, 31, 33, 35, 37-47, 49-50, and 52 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims recite a genus of compounds that is defined only by the fact that they are “derivatives” of cyclopamine or by their biological activity, *e.g.*, “another compound that specifically inhibits Hedgehog/Smoothened signaling” or “said compound exerts receptor-binding properties similar to cyclopamine and bind to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling”). There is insufficient written description of the claimed compounds, other than cyclopamine and jervine as disclosed in the specification. The lack of written description of the instantly claimed compounds is further compounded by the fact that the compounds as instantly claimed must not only be derivatives of cyclopamine, but must also possess receptor-binding properties similar to cyclopamine. Accordingly, other than cyclopamine and jervine, Applicants have not demonstrated possession of the claimed “derivatives” of cyclopamine or “another compound that specifically inhibits Hedgehog/Smoothened signaling” or compounds that exert “receptor-binding properties similar to cyclopamine and bind to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling” as recited in the instant claims.

Aside from the very limited group of compounds disclosed in the specification (*e.g.*, cyclopamine and jervine), Applicants provide no direction as to (a) what subset of compounds out of all possible compounds that exist in the art would have been reasonably expected to a) specifically inhibit Hedgehog/Smoothened signaling or exert receptor binding properties similar to cyclopamine and (b) which of those compounds actually *has* activity in inhibiting Hedgehog/Smoothened signaling or exerts receptor binding properties similar to cyclopamine without having to execute hit or miss testing practices in order to make such a determination.

Although general techniques such as cellular assays may be known in the art (as acknowledged by Applicants in their response and in the 1.132 Declarations filed 12/18/2007), this fact fails to diminish the amount of experimentation that the skilled artisan would have to undertake to even identify, let alone determine the full scope of the claimed "derivatives" of cyclopamine or "another compound that specifically inhibits Hedgehog/Smoothened signaling" or compounds that exert "receptor-binding properties similar to cyclopamine and bind to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling" as recited in the instant claims, particularly in view of the fact that this genus as a whole is not one that is well-known or well-defined in the art such that the skilled artisan would readily envision those compounds that are within the scope of the claimed genus.

The need for testing amongst varying species of compounds to determine the full scope of the genus of antagonists instantly claimed demonstrates that Applicants were not in possession of the full scope of the genus now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Despite the disclosure cyclopamine and jervine, it remains that the specification provides non-limiting exemplification of a solely functional genus of agents that may be used within the context of the present invention. With the exception of cyclopamine and jervine as disclosed in the original disclosure and claims, Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other agents that may have any of the disclosed functions, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other agents that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such compounds, and, therefore, did not have written description of the full scope of the genus claimed.

Further, though Applicants have limited the claimed agents to those that perform a particular function, e.g., those that specifically inhibit Hedgehog/Smoothened signaling or exert "receptor-binding properties similar to cyclopamine and bind to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling", it remains that Applicants have not appropriately defined the metes and bounds of the genus, even when limited by function (step-plus-function form). As taught in the MPEP at § 2163, step-plus-function claims are not adequately described if "the written description adequately links or associates adequately described particular structure, material or acts to the function recited in a step-plus-function claim limitation," or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation." The instant application fails to meet these criteria. The present specification provides no disclosure beyond the generic disclosure of the required function that would correlate a common structural element or material to performance of the claimed function and that would be readily identifiable to one of skill in the art.

Claims 47-49 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description"

Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

The recitation of "non-tumoral skin disorder" as recited in claim 47 and claims dependent from claim 47 lacks adequate written description because, other than psoriasis, Applicants have not described any other non-tumoral skin disorders as recited in the instant claims. The teachings of the specification as filed provide, at best, a mere "wish or plan" to uncover additional skin disorders that might be able to be treated as claimed.

Claims 47-49 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

*In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA

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[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of a "non-tumoral skin disorder presenting skin lesions" comprising administering cyclopamine "or another compound that specifically inhibits Hedgehog/Smoothened signaling".

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

In the instant case, Applicants contemplate treating any non-tumoral skin disorder presenting skin lesions. However, there is no evidence of record that cyclopamine or "another compound that specifically inhibits Hedgehog/Smoothened signaling" has any therapeutic benefit in any non-tumoral skin disorder presenting skin lesions, other than psoriasis. As such, given the divergent pathologies of skin disorders encompassed by the claims, of which there is no evidence of record that Hedgehog/Smoothened signaling is implicated, it is entirely unpredictable what non-tumoral skin disorders presenting skin lesions might be reasonable treatable using the claimed methods.

2. The breadth of the claims

The claims are broad insofar as they disclose the treatment of any non-tumoral skin disorder presenting skin lesions with the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various skin disorders encompassed by the claims, particularly in humans. The direction concerning treating patients having psoriasis is found in the specification at pages 15-17. Applicants also describe formulations at pages 15-17. Doses required to practice their invention are described at page 15. A 100,000-fold range of doses is recommended (*e.g.*, 0.001 to 100 mM). Since only cyclopamine as instantly claimed has ever been used to treat any human non-tumoral skin disorder presenting skin lesions (psoriasis), how is the skilled physician to know what dose to use for each of these pathologically different disorders and structurally diverse compounds?

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for non-tumoral skin disorders other than psoriasis as inferred in the claims and contemplated by the specification.

*Genentech Inc. vs. Nova Nordisk* states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because cyclopamine is effective to treat psoriatic lesions then all other compounds that have a similar mechanism of action must therefore, *a priori*, be useful in the treatment of other non-tumoral skin disorders. However, the claims encompass a multitude of compounds defined only by their biological activity. Applicants tested one compound (cyclopamine) in the treatment of psoriatic lesions. The instant claims recite the treatment of a subject having "a non-tumoral skin disorder presenting lesions" comprising administering to the subject cyclopamine or "another compound that specifically inhibits Hedgehog/Smoothened signaling". However, the disclosure and claims leave it to the skilled artisan to work out which compound is to be used to treat which non-tumoral skin disorder and what amount of medicament is to be used to produce the therapeutic result of "treating a subject".[2] This is a classic case of undue experimentation.

Determining if any particular claimed compound would treat any particular non-tumoral skin disorder would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants and the broad scope of the claims.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 50-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Keeler (Proceedings of the Society for Experimental Biology and Medicine, 1975, vol. 149, pages 302-306) (cited by Applicants in IDS filed 10/18/2004; Reference "CC").

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[2] This is especially true given the fact that Applicants recommend a 100,000-fold range of doses of cyclopamine (*e.g.*, 0.001 to 100 mM)

The prior art teaches administration of daily doses of 10, 20, 30, 60, or 90 mg of cyclopamine or jervine to rats, mice, and hamsters, thus meeting the limitation "administration" as recited in the instant claims (Table 1). The prior art is silent with respect to the instantly claimed effect of such administration (*i.e.*, downregulation of epidermal growth factor receptor expression in epidermal cells), however the method steps of the reference and those instantly claimed are identical.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Though Keeler does not expressly teach downregulation of epidermal growth factor receptor expression in epidermal cells (claim 50) as a result of the administration of the disclosed compounds to the subject, the administration of the same compound(s) as claimed (*e.g.*, those identical to Applicants' claimed compounds) to the same host as claimed is considered to necessarily have the claimed effect of downregulation of epidermal growth factor receptor expression in epidermal cells on the subject being treated, whether expressly recognized by Keeler or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

## *Allowable Subject Matter*

Claims 32, 34, and 36 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

## *Conclusion*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 2002/0165221 A1 (Published Nov. 7, 2002; Filed Oct. 12, 2001) discloses methods of inhibiting aberrant growth states resulting from *hedgehog* gain-of-function, *ptc* loss of function or *smoothened* gain-of-function comprising administering a hedgehog antagonist.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614